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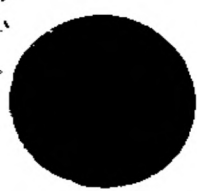
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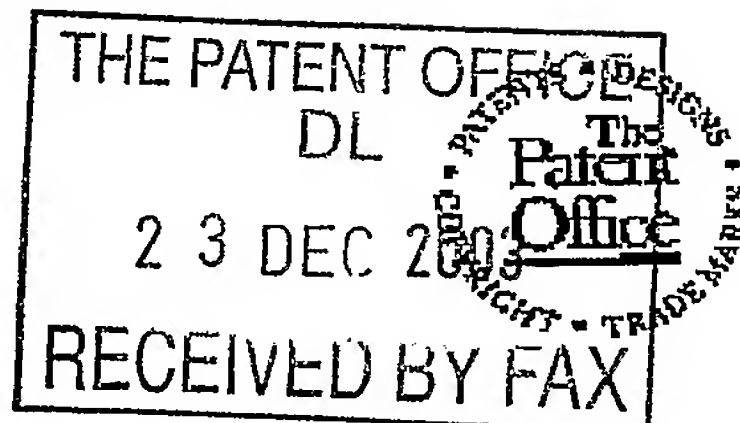
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## 0329812.2

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0886667S001

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Patents ADP number (if you know it)

If the applicant is a corporate body, give the
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4. Title of the invention

ROMP POLYMER SYNTHESIS

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom
to which all correspondence should be sent
(including the postcode)

ROLLINS, Anthony, John; HAMMER, Catriona, MacLeod;
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Patents ADP number (if you know it)  081893375004

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Request for a preliminary examination
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Request for a substantive examination
(Patents Form 10/77)

Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature(s)  ROLLINS, Anthony, John        A. J. Rollins       Date  23 December 2003

12. Name, daytime telephone number and
    e-mail address, if any, of person to contact in
    the United Kingdom

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## ROMP Polymer Synthesis

### Technical Field of the Invention

The present invention relates to the field of solid-phase radiochemistry.  More

specifically, the present invention relates to solid phase radiochemistry carried out on

5  the internal surfaces of a device wherein said internal surfaces are coated with a ring-

opening metathesis polymerisation (ROMP) polymer.

### Description of Related Art

Ring-opening metathesis polymerisation (ROMP) is a variant of the olefin metathesis

reaction.  One of the main advantages of ROMP polymers is that in principle every

10  monomer unit carries a functional group and should give much higher loading than

some other polymers.  ROMP is known for the production of functionalised polymers for

organic synthesis (Barrett *et al* Chemical Reviews 2002 **102** pp 3301-24).  A number of

other chemical applications have been reported, e.g. chromatography, solid-phase

extraction, construction of synthetic libraries and purification, all of which are discussed

15  by Barrett *et al*.

The application of ROMP polymers to the surfaces of devices has also been reported.

In WO 03/093406 ROMP polymers are suggested as a means to alter the surfaces of a

miniaturised bioreactor to render them more biocompatible, i.e. that the cell viability and

proliferation and/or other biological components produced by the cells are not adversely

20  affected by contact with the surface.

In US 2002/0122747 microdevices are fabricated with ROMP polymers in order to

enable metallization of the surfaces.  The side chains of the ROMP polymer are

selected such that they bind to the desired metal.  The integration of components such

as electrodes, heaters and valves is therefore permitted, rendering the microdevice

25  more functional.

### Summary of the Invention

The present invention involves the application of ROMP polymers to the internal

surfaces of a device for the purpose of carrying out a solid-phase radiochemical process

within the device.  An additional embodiment of the invention is an automated synthesis

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system comprising a number of devices of   the invention in order that a series of processes can be carried out in direct sequence.  In a preferred embodiment, the present invention is a microfabricated device.

**Detailed Description of the Invention**

5      In a first aspect, the present invention relates to a device adapted to carry out a solid-phase radiochemical process characterised in that the solid-phase radiochemical process is carried out on the internal surfaces of said device wherein said internal surfaces are coated with a Ring Opening Metathesis Polymerisation (ROMP) polymer.

A "device adapted to carry out a solid-phase radiochemical process" may comprise one

10     or more components, e.g. a laboratory vessel made from glass, glassy carbon or a metal such as stainless steel, a well of a microplate, polymer tubing or a microfabricated device.  Due to the radioactive nature of the process, such devices are provided with shielding to protect the operator from radioactive contamination.  Such shielding suitably takes the form of a lead barrier or box around the device.  Furthermore, the devices

15     according to the invention are suitably connected to or incorporate a means of radiochemical detection, for example a positron detector or HPLC system fitted with a radioactivity detector.

The "internal surface" of the device is taken to mean the surface that comes into contact with the reactants introduced into the device.  Therefore, when the internal surface is

20     coated with a ROMP polymer, the reactants come into contact with the side chains of the ROMP polymer.  The side chains themselves participate in the chemical process, and because they can be virtually any organic substituent the polymer can be tailored to be suitable for carrying out a specific chemical process.

"ROMP polymer" is defined in the present invention as a polymer obtained by the

25     ROMP reaction.   The ROMP reaction uses strained cyclic olefins to produce stereoregular and monodisperse polymers and co-polymers.  The mechanism of ROMP reaction involves an alkylidene catalyst and is identical to the mechanism of olefin synthesis except that, as the reaction involves a cyclic olefin, the new olefin that is generated stays attached to the catalyst as part of a growing polymer chain as

30     illustrated below:

3
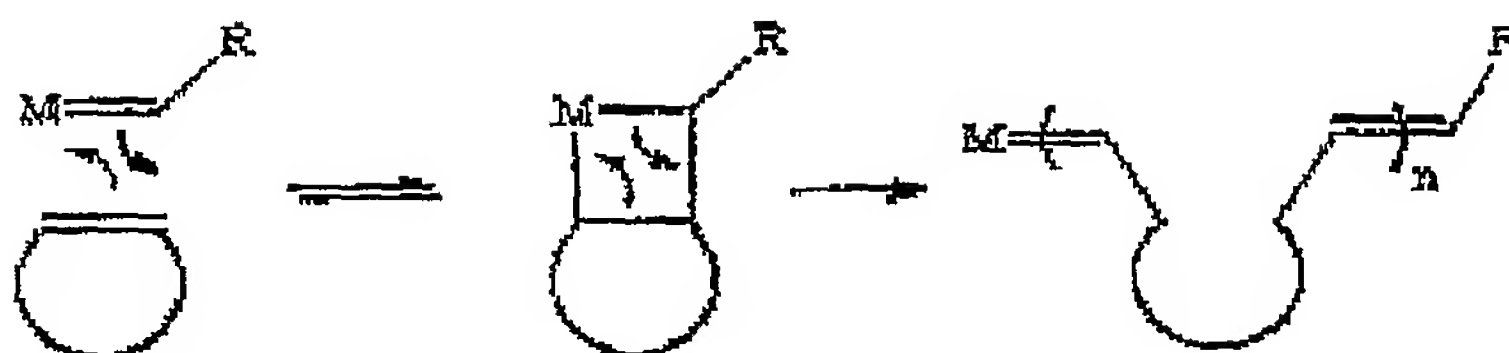


Wherein M is a metal selected from molybdenum and ruthenium and R is an organic substituent.

5   The driving force of the ROMP reaction is the relief of the strain on the ring such that the second step in the reaction above is essentially irreversible. Strained cyclic olefins such as those illustrated below have sufficient ring strain to make the reaction possible:



A preferred ROMP polymer of the present invention is of Formula I:



(I)

10

wherein:

X is either a $C_{1-6}$ hydrocarbon chain or a $C_{4-6}$ alicyclic group;

$R^1$ is selected from hydrogen, hydroxyl, halogen, nitro, cyano, -SH, -N=C=O, $C_{1-20}$ alkyl, $C_{4-12}$ aryl, $C_{3-20}$ alkylaryl, $C_{2-20}$ acyl, $C_{2-20}$ functionalised acyl, $C_{1-20}$ formyl,

15   $C_{1-20}$ functionalised formyl, $C_{1-20}$ alkoxy, $C_{1-20}$ functionalised alkoxy, $C_{1-20}$ amino, $C_{1-20}$ functionalised amino, $C_{3-18}$ trialkylammonium, $C_{3-18}$ trialkylammonium with bound fluoride ion, $C_{1-20}$ imino, $C_{1-20}$ functionalised imino, $C_{1-20}$ amido, $C_{1-20}$ functionalised amido, $C_{1-20}$ nitroalkyl, $C_{1-20}$ functionalised nitroalkyl, $C_{1-20}$ carboxyl, $C_{1-20}$ functionalised carboxyl, carbonate, $C_{2-20}$ carboalkoxy or $C_{2-20}$

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functionalised carboalkoxy or $R^1$ optionally further comprises a radiotracer precursor, a catalyst or an enzyme;

5   -(L)$_y$- is linker group wherein each L is independently -CY$_2$- , -CY=CY- , -C≡C- , -CY$_2$CO$_2$- , -CO$_2$CY$_2$- , -NYCO- , -CONY- , -NY(C=O)NY-, -NY(C=S)NY-, -SO$_2$NY-, -NYSO$_2$- , -CY$_2$OCY$_2$- , -CY$_2$SCY$_2$- , -CY$_2$NYCY$_2$- , a C$_{4-8}$ cycloheteroalkylene group, a C$_{4-8}$ cycloalkylene group, a C$_{5-12}$ arylene group, or a C$_{3-12}$ heteroarylene group, or an amino acid, wherein Y is independently chosen from H, C$_{1-4}$ alkyl, C$_{2-4}$ alkenyl, C$_{2-4}$ alkynyl, C$_{1-4}$ alkoxyalkyl or C$_{1-4}$ hydroxyalkyl and y is an integer of value 0 to 10; L is optionally further substituted with one or more $R^2$ groups

10   where $R^2$ is selected from hydrogen, hydroxyl, halogen, nitro, cyano, -SH, — N=C=O, C$_{1-20}$ alkyl, C$_{4-12}$ aryl, C$_{3-20}$ alkylaryl, C$_{2-20}$ acyl, C$_{2-20}$ functionalised acyl, C$_{1-20}$ formyl, C$_{1-20}$ functionalised formyl, C$_{1-20}$ alkoxy, C$_{1-20}$ functionalised alkoxy, C$_{1-20}$ amino, C$_{1-20}$ functionalised amino, C$_{3-18}$ trialkylammonium, C$_{1-20}$ imino, C$_{1-20}$ functionalised imino, C$_{1-20}$ amido, C$_{1-20}$ functionalised amido, C$_{1-20}$ nitroalkyl, C$_{1-20}$

15   functionalised nitroalkyl, C$_{1-20}$ carboxyl, C$_{1-20}$ functionalised carboxyl, carbonate, C$_{2-20}$ carboalkoxy or C$_{2-20}$ functionalised carboalkoxy; and,

n = number of polymer units.

"Alkyl" used either alone or as part of another group is defined herein as any straight, branched or cyclic, saturated or unsaturated C$_x$H$_{2x+1}$ group.

20   "Aryl" used either alone or as part of another group is defined herein as any C$_{6-14}$ molecular fragment or group which is derived from a monocyclic or polycyclic aromatic hydrocarbon. Suitable aryl groups of the invention include, but are not limited to, haloaryl, alkylaryl, arylcarbamyl, phenylazo, arylamino, arylthio, toluene, benzoic acid, phenol, arylsulfinyl, arylsulfonyl, arylsulfonamido, benzothiophene, naphthalene,

25   quinoline, isoquinoline, pyridine, pyrimidine, and pyrazine.

$R^1$ is preferably halogen, C$_{1-20}$ alkyl, C$_{4-12}$ aryl, C$_{3-20}$ alkylaryl, C$_{1-20}$ amine, C$_{1-20}$ functionalised amine, C$_{1-20}$ carboxylic acid, C$_{1-20}$ functionalised carboxylic acid or a group comprising an enzyme.

5

$R^1$ is most preferably trialkylammonium;     trialkylammonium with bound $^{18}$F-fluoride ion; $C_{1-20}$ alkyl; -N=C=O; or -SH, or comprises an enzyme or a catalyst.

It is additionally suitable for more than one particular $R^1$ group to be present in the ROMP polymer of the invention. This is achieved by the inclusion of more than one
5   type of monomer in the reaction mixture and enables the swelling properties of the resultant polymer to be tailored as well as the production of a dual- or multi-capacity device.

A most preferred ROMP polymer of the present invention is of Formula II:



(II)
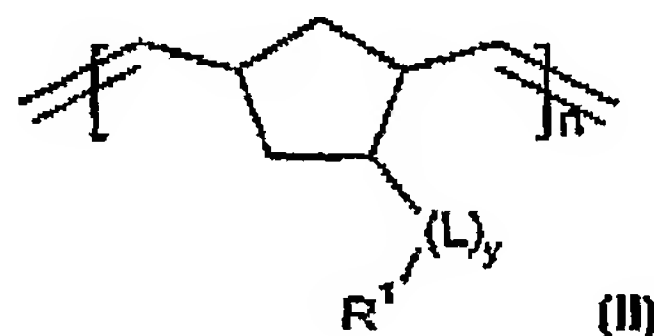
10         wherein:

-(L)$_y$-, $R^1$ and n are as defined in claim 2 for Formula I.

An especially preferred ROMP polymer of the present invention is of Formula III:
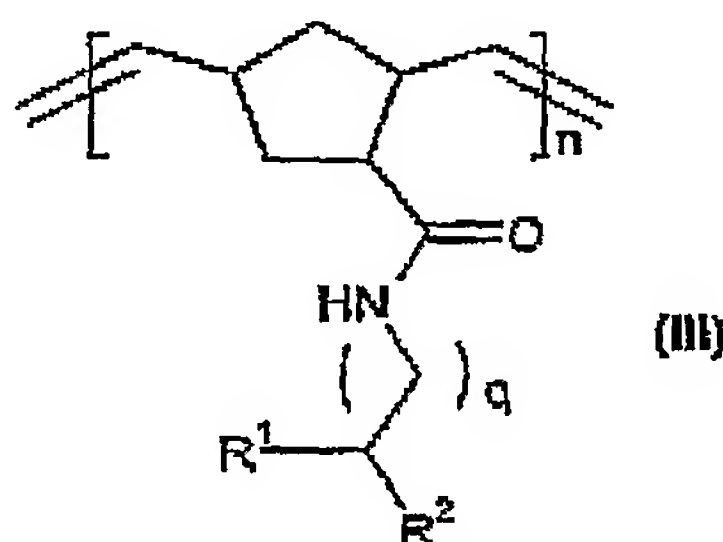


(III)

wherein:

15         $R^1$ and n are as defined in claim 2 for Formula I;

$R^2$ is an optional group as defined in claim 2 for -(L)$_y$- of Formula I; and,

q = 1-4.

6

A most especially preferred ROMP polymer of the present invention is of Formula III wherein $R^1$ is trialkylammonium, $R^2$ is absent, q = 3 and n = number of polymer units. When $R^1$ of Formula III is trialkylammonium, the device is particularly suitable for the recovery of $^{18}F$-fluoride ion from $^{18}O$-enriched water containing $^{18}F$-

5   fluoride ion, or natural water containing $^{18}F$-fluoride ion, as shown in the scheme below:
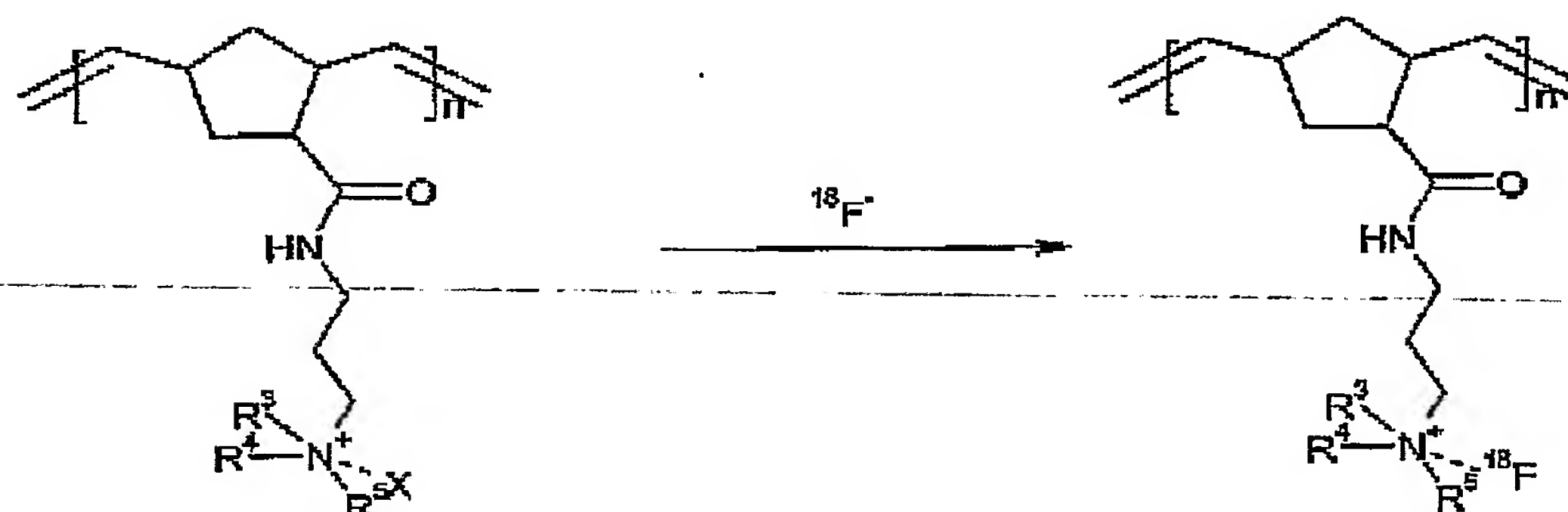


wherein $R^3$-$R^5$ are $C_{1-6}$ alkyl groups and X is a non-nucleophilic anion, e.g. carbonate, bicarbonate or oxalate.

$R^1$ of Formula III then becomes trialkylammonium with bound $^{18}F$-fluoride ion, which
10   renders the device particularly suitable for carrying out *in situ* radiofluoridations.

Preferably, the *in situ* radiofluoridation forms a step in the synthesis of an $^{18}F$-labelled radiotracer. The term "radiotracer" as used herein includes carrier-added and no carrier-added radiolabelled compounds, and in particular includes radioligands (compounds radiolabelled at high specific activity).

15   The skilled person will appreciate that use of other suitable R groups will enable immobilisation of other radiolabels of interest and their subsequent use for *in situ* radiolabelling reactions. Examples of other suitable radiotracer labels that can be immobilised for *in situ* radiolabelling reactions include: other non-metal positron emitters such as $^{11}C$, $^{13}N$, $^{15}O$, $^{17}F$, $^{75}Br$, $^{76}Br$ or $^{124}I$; positron-emitting radioactive metals such as
20   $^{64}Cu$, $^{48}V$, $^{52}Fe$, $^{55}Co$, $^{94m}Tc$ or $^{68}Ga$; gamma-emitting radioactive halogens such as $^{123}I$, $^{125}I$, $^{131}I$ or $^{77}Br$; and gamma-emitting radioactive metal ions such as $^{99m}Tc$.

Specific examples of $^{18}F$-labelled radiotracers which may be prepared using the ROMP polymer of Formula III where $R^1$ is trialkylammonium with bound $^{18}F$-fluoride ion, $R^2$ is

absent, q = 3 and n = number of polymer units, include: 2-[$^{18}$F]fluorodeoxyglucose (2-[$^{18}$F]-FDG); L-6-[$^{18}$F]fluoro-DOPA; 3'-deoxy-3'-fluorothymidine (FLT); 2-(1,1-dicyanopropen-2-yl)-6-(2-[$^{18}$F]fluoroethyl)-methylamino)-naphthalene ([$^{18}$F]FDDNP); 5[$^{18}$F]fluorouracil; 5[$^{18}$F]fluorocytosine; and, [$^{18}$F]-1-amino-3-fluorocyclobutane-1-carboxylic acid ([$^{18}$F]-FACBC). In each case, an unlabelled precursor compound of the $^{18}$F-labelled radiotracer is introduced into the device. $^{18}$F becomes incorporated into the precursor compound via nucleophilic substitution to form the $^{18}$F-labelled radiotracer as illustrated below:
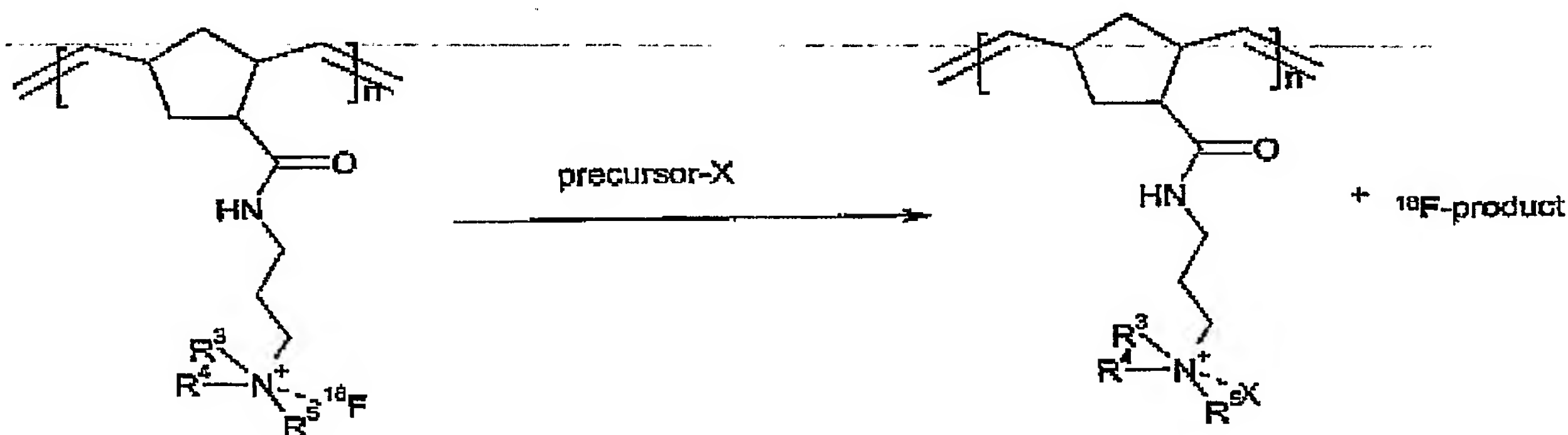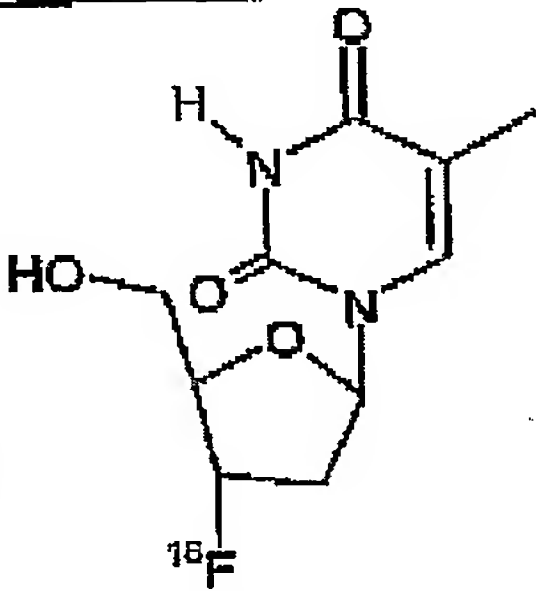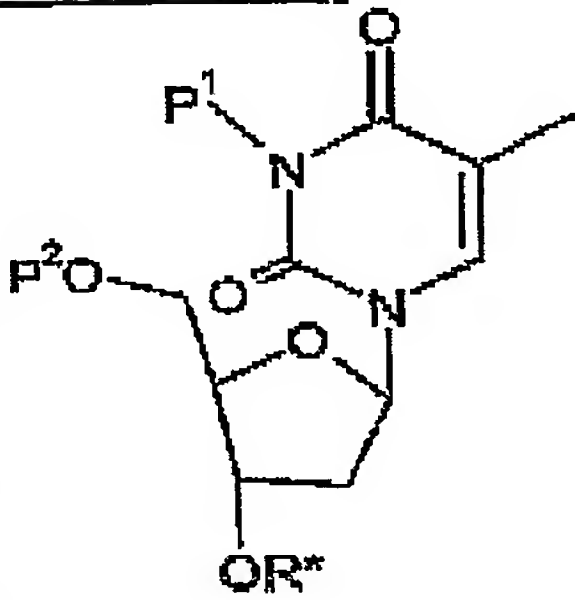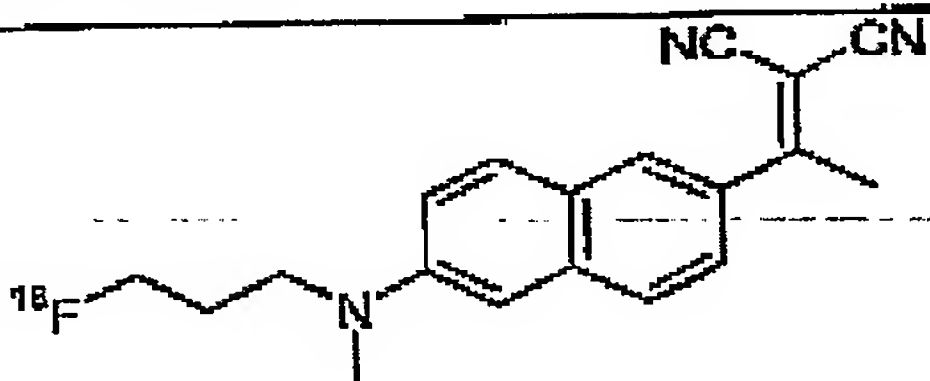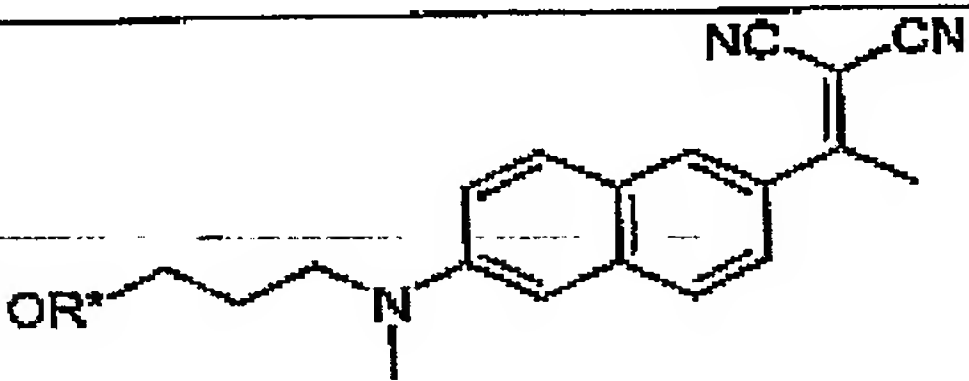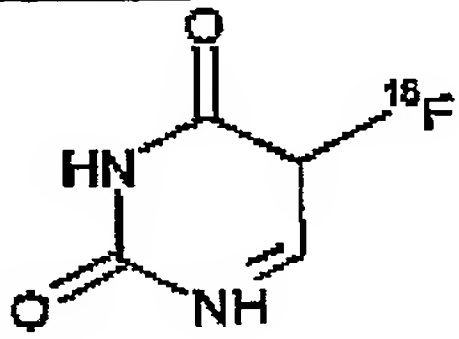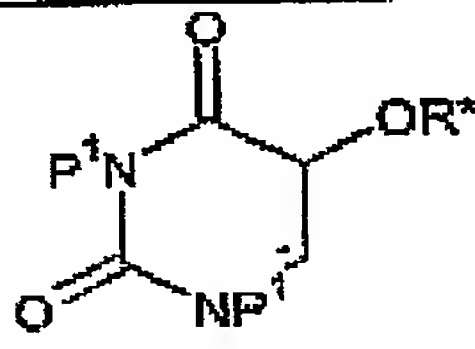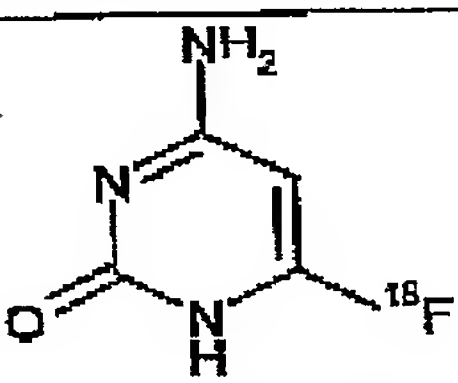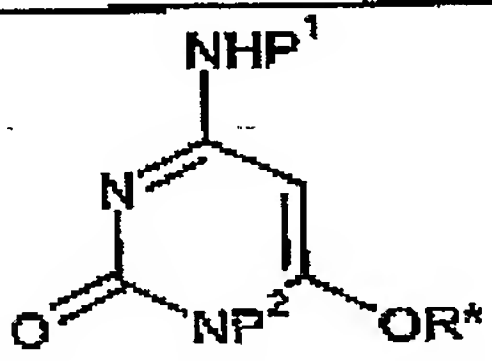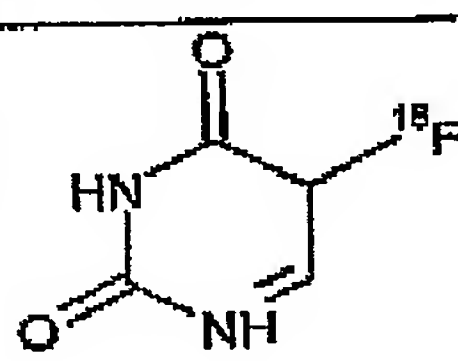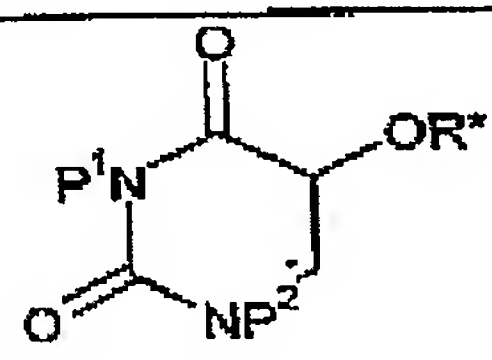


wherein $R^3$-$R^5$ are $C_{1-6}$ alkyl groups and X is a non-nucleophilic anion, e.g. carbonate, bicarbonate or oxalate.

The structures of various $^{18}$F-labelled radiotracers and suitable precursors for their synthesis are given in Table I:

Table I

| $^{18}$F-labelled radiotracer | Precursor |
|---|---|
| 2[$^{18}$F]FDG | |
|  |  |
| [$^{18}$F]FLT | |

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[$^{18}$F]FDDNP

5[$^{18}$F]fluorouracil

5[$^{18}$F]fluorocytosine

[$^{18}$F]-FACBC

In Table I above, R* is triflate or nonaflate and P¹-P⁴ are each a protecting group.
Suitable protection may be achieved using standard methods of protecting group
chemistry. After the fluoridation is complete, any protecting groups may be removed by
simple procedures which are also standard in the art. Suitable protection and

5   deprotection methodologies may be found, for example, in Protecting Groups in Organic

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Synthesis, Theodora W. Greene and Peter G. M. Wuts, published by John Wiley & Sons Inc.

It will be appreciated by those skilled in the art that production of radiotracers may also be suitably carried out on a device wherein $R^1$ of Formulae I-III comprises the

5   radiotracer precursor. Radioabelling is achieved by introducing the radiolabel into the device, such that the radiolabelled product becomes detached from the polymer once radiolabelling has taken place successfully.

When $R^1$ of any of Formulas I to III is a $C_{1-20}$ alkyl group, the device is particularly suitable for performing chromatographic separations. A preferred side chain is a C18

10  hydrocarbon as this is the most commonly used side chain for reverse-phase chromatography, which is a chromatographic technique in which analytes bind non specifically through hydrophobic interaction. The bound analytes can be eluted by gradient elution using a solution of ever increasing or decreasing polarity.

When $R^1$ of any of Formulas I to III is a group comprising an enzyme, the device is

15  particularly suitable for carrying out enzymatic reactions. With the enzyme immobilised on the ROMP polymer there is no necessity to have a separate step in the process for the removal of enzyme from the reaction mixture. An example reaction is the conversion of $^{11}C$-thymine to $^{11}C$-thymidine wherein thymidine phosphorylase is immobilised into the ROMP polymer. It will be appreciated that many other enzymatic

20  reactions can be carried out in this way.

When $R^1$ of any of Formulas I to III is -SH, the device is particularly suitable as a scavenger, e.g. for taking up mercury ions from a solution.

A particularly preferred embodiment of the device of the present invention is a microfabricated device.   In microfabricated devices, predetermined networks of

25  microchannels or capillaries, typically 10-300$\mu$m, more typically 50-300$\mu$m in diameter, are etched or otherwise machined on the surface of a substrate, suitably made of glass or silicon. Alternatively, the microchannels may be created using polydimethylsiloxane, which may be poured over a master (usually glass), allowed to cure and then peeled off, or are fabricated by injection moulding, hot embossing, casting, lithography, or

30  machining. These channels may be sealed through bonding of a cover plate, suitably

10

made from a metal (for example, gold, platinum or silver) or , more commonly, glass, creating a contained network capable of manipulating picolitre to microlitre volumes of liquid or gas. The sealing method used depends on the materials selected and may be selected from thermal bonding (for glass chips), anodic bonding (for silicon

5    chips), and for polymer chips the sealing method may be selected from clamping, gluing, application of heat and pressure, and natural adhesion. Nanolitre and picolitre volumes may be used for analytical aspects but the devices can handle flows of up to hundreds of microlitres per minute. This could be increased further, for example, by stacking multiple devices. These devices are designed to be used either with micro

10   syringe pumps (available from Kloehen Limited, Las Vegas, USA) or under electroosmotic flow. Fused silica capillaries can be used for interfacing with reagents or reagent sources and analytical systems (such as ultraviolet (UV), capillary electrophoresis (CE), capillary electrochromatography (CEC), electrochemical, refractive index, and radioactivity detectors).

15   A second aspect of the present invention is a method for the production of a microfabricated device of the invention comprising:

    (i)      creating a defined network of microchannels within said device;

    (ii)    heating the device to a temperature of between 80°C and 140°C; and,

    (iii)     passing a solution of monomer, crosslinker and catalyst through the
20                microchannels while concurrently introducing a flow of nitrogen through the
             microchannels such that ROMP polymer is deposited on walls and
             indentations of the microchannels.

Step (i) above may comprise the following steps:

(a) providing a suitable substrate;

25   (b) marking a specific pattern onto the surface of said substrate;

(c) etching the pattern into the surface of said substrate; and

(d) attaching a cover to the etched surface of step (c) thereby forming channels.

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Alternatively, step (i) can comprise the use   of a polymer in a process selected from injection moulding, hot embossing, casting, lithography or machining.

In a third aspect of the present invention, it is envisaged that a number of such microfabricated devices could be fluidly interconnected to form an automated synthesis

5    system.  A series of solid-phase radiochemical processes can be carried out within the system, e.g. a mixing and reaction device followed by an analysis device and finally a separation device.  Such an automated synthesis system would enable the complete automation of a series of solid-phase radiochemical processes.  This is desirable as it means (i) minimum user contact with radioactive reactants and (ii) the process takes as

10    little time as possible thereby achieving a high specific activity product.

In a fourth aspect, the present invention relates to the use of the device of the invention for:

(i)    recovery of radioisotopes;

(ii)    radiochemical synthesis; or

15    (iii)    radiochemical purification.

In a fifth aspect, the present invention relates to a process for labelling the precursor of a radiotracer with a radiolabel characterised in that the radiolabel is provided bound to a ROMP polymer.  Suitable radiolabels are positron emitters such as $^{18}F$ and $^{11}C$; gamma-emitting radioactive halogens such as radioiodine; and, radioactive metal ions

20    such as $^{99m}Tc$.

**Brief Description of the Examples**

Example 1 describes the synthesis of ROMP monomer suitable for preparing a ROMP polymer for fluoride (ion-exchange) extraction.

Example 2 describes the synthesis of the cross-linker used in the reaction to polymerise

25    the monomer prepared in Example 1.

Example 3 describes the synthesis of tertiary amine ROMP polymer.

12

The results of Example 4 show that the          synthesized ROMP resin can be used for
the successful removal of $^{18}$F-fluoride from aqueous media (such as that obtained from
the cyclotron target).  Furthermore the fluoride can be removed from the resin (in yields
of up to 80 %) by flushing the resin with $K_2CO_3$ (aq).  Lastly it has been shown that the

5   performance of the ROMP resin is at least equivalent if not superior to what is arguably
the industrial standard solid phase for this application.

Example 5 relates to the cartridge testing of ROMP fluoride extraction polymer for
extraction of fluoride from target water.

Example 6 describes a process for the production of [$^{18}$F]FDG on a microfabricated

10   device.

Example 7 relates to the creation of a predetermined network of microchannels on the
surface of a glass, silicon or polymer substrate.

Example 8 relates to coating the surfaces of a microfabricated device with ROMP
polymer having tetraalkylammonium side chains.

15   Example 9 describes a process used for the recovery of [$^{18}$F]fluoride from $^{18}$O-enriched
water using the device of the present invention.

**Brief Description of the Figures**

Figure 1 illustrates the reaction scheme used for synthesis of ROMP monomer for
fluoride (ion-exchange) extraction.

20   Figure 2 shows the chemical structure of the synthesised cross-linker.

Figure 3 illustrates the reaction scheme used for synthesis of tertiary amine ROMP
polymer.

Figure 4A illustrates the chemical structures of tertiary amine resin, quaternary-
ammonium resin, and QMA resin.

25   Figure 4B illustrates the set up used for testing ROMP fluoride extraction polymer for
extraction of fluoride from target water.

Figure 4C shows the extraction of $^{18}$F- fluoride from aqueous media *via* the process of ion-exchange.

Figure 5 illustrates the set up for conducting cartridge testing of ROMP fluoride extraction polymer for extraction of fluoride from target water.

5    Figure 6A illustrates the radiofluoridation of the precursor of [$^{18}$F]-FDG. Ac represents an acyl protecting group.

Figure 6B illustrates a sample radio-HPLC trace of the radiochemical composition of the collection vial contents obtained following radiofluoridation of the precursor of [$^{18}$F]-FDG on a microfabricated device.

10   Figure 6C illustrates the change in behaviour of the resin over time (despite conditioning prior to each experiment) and a trend to ever less efficient fluoride extraction.

Figure 7 illustrates the steps involved in the creation of a predetermined network of microchannels on the surface of a glass, silicon or polymer substrate.

Figure 8 shows the synthesis of a ROMP polymer having a tetraalkylammonium side
15   chain, wherein $R^3$ to $R^5$ are independently $C_{1-6}$ alkyl groups.

Figure 9 is a schematic diagram showing how the polymerisation is carried out in the microchannels of a microfabricated device. The centre flow (white) is the gas (from a regulated cylinder) and the liquid flow (black) through the side indentations(from syringe pumps) is the ROMP polymer reaction mixture.

20   Figure 10 shows a schematic of a microfabricated device as well as micrographs at x25 and x100 of the microchannels coated with ROMP polymer.

Figure 11 illustrates retention of [$^{18}$F]-fluoride on the polymer on a microfabricated device through ion exchange following introduction of an aqueous solution of [$^{18}$F]fluoride. $R^3$ to $R^5$ are independently $C_{1-6}$ alkyl groups.

25   *Example 1:  Synthesis of ROMP monomer for fluoride (ion-exchange) extraction*

The reaction scheme is illustrated in Figure 1.

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## (a)    Preparation of Acid Chloride

To 10g (72 mMol) of Norbornene carboxylic acid **1** was added 10.4 ml of Thionyl
Chloride **2** (17g or 144mMol). The mixture was stirred under a nitrogen atmosphere for
2 hours (Reaction mixture is a clear Champaign coloured liquid).

5    Excess Thionyl chloride was then removed on a rotary evaporator by the addition of
aliquots (4 x 6 ml) of toluene at approximately $45^0C$. The acid chloride **3** could be stored
for up to a week before use providing it was kept refrigerated and under nitrogen.

## (b)    Reaction of Acid Chloride with Amine

To the acid chloride **3** was added 15 ml DCM and the mixture chilled on ice.  0.8
10   equivalents (5.92g, 58 mMol, 7.3 ml) of amine **4** were then added drop-wise with
stirring. The reaction mixture was then allowed to reach RT and left to react for a further
two hours. This entire procedure was performed under a nitrogen atmosphere (After
amine addition reaction mixture appears as an opaque honey colour solution containing
white precipitate).

15   ## (c)    Purification of crude monomer mixture

After the two hours reaction time the reaction mixture was extracted with 3 x 10 ml of 30
% v/v conc. $H_3PO_4$ (pH ~2). The combined aqueous components were then adjusted to
pH 12 using conc. NaOH(aq) and extracted with 4 x 12 ml DCM. The combined DCM
fragments were dried over $MgSO_4$, filtered and the DCM removed under reduced
20   pressure to yield the purified monomer **5** (11.2 g heavy golden oil, 87%).

Elemental C:H:N analysis gave 64.99% C, 9.34% H and 11.30% N. (expected values
calculated from $C_{13}H_{22}N_2O$. formula weight = 222 were 70.23% C, 9.97% H and 12.60%
N).

### Example 2:  Synthesis of cross-linker

25   Figure 2 shows the chemical structure of the synthesised cross-linker.

To a stirred solution of 1,4-Diiodo-benzene (9.90 g, 30 mMol), norbomadiene (35 ml,
325 mMol), piperidine (14.9 ml, 50 mMol) and $(AcO)_2(PPh_3)_2Pd(II)$ (0.674 g, 3 mMol) in

15

DMF (45 ml) was added dropwise formic     acid (3.46 ml, 63 mMol). A considerable amount of heat was evolved and the mixture went into solution. The reaction was followed using TLC (hexane mobile phase on silica, $R_{f(cross\ liker)}$ = 0.5). Spots were elucidated using UV. After 41 hrs the reaction was quenched with water (200 ml) and

5    the resulting mixture extracted with hexane (4 x 100 ml). The combined organic phase was washed with 10 % NaOH (3 x 100ml), 10 % $H_3PO_4$ (3 x 100 ml), water (3 x 100 ml) and saturated brine (1 x 100 ml). The organic phase was then dried over $MgSO_4$ and concentrated to give a dark red oil.

Purification was achieved in two stages via silica chromatography (hexane). A short

10   primary column removed the dark red impurity ($R_f$ = 0-0.1) to give a colourless oil. Further purification on a larger column yielded 3.64 g of a white solid 1 (46 %).

Mass spectrometry (El +ve mode) of the product gave a peak at $m/z$ = 262 $[M]^+$. Elemental C:H analysis gave 91.51% C and 8.63% H (expected values calculated from $C_{20}H_{22}$, formula weight = 262 were 91.55% C, 8.45% H). $^1H$-NMR in $CDCL_3$, δ(ppm)

15   relative to tetramethylsilane (TMS): 7.2 (s, 4H, Aryl-CH), 6.2 (d m, 4H, Vinyl-CH), 2.95 (broad s, 2H, allylic-CH), 2.88 (broad s, 2H, allylic-CH), 2.7 (m, 2H, benzylic-CH).

**Example 3:   Synthesis of tertiary amine ROMP polymer**

Figure 3 illustrates the reaction scheme used for synthesis of tertiary amine ROMP polymer.

20   To a 50 ml round bottom flask was added monomer 1 (2 g, 9 mMol), cross linker (0.262 g, 1 mMol), THF (12 ml) and DCM (2 ml). The contents of the flask were then mixed thoroughly and flushed with nitrogen. To this solution was added catalyst (0.09 g, ~1%) in DCM (1 ml) and again the contents mixed. The static reaction mixture was then left under an inert atmosphere at 40 °C for one hour.

25   After one hour the crude resin product (translucent brown gel) was broken into several fragments with a spatula and 20 ml of the following mixture was added: 75% THF, 20% $CH_3CN$ and 5 % Ethyl Vinyl Ether. A condenser was then fitted and the mixture was refluxed at 120 °C under nitrogen for 1 hr. The resin was then transferred to a glass funnel with a frit and washed with sequential THF (20 ml) followed by diethyl ether (20

30   ml) a total of three times before being dried under vacuum. The dried resin product 3

appears as a mottled brown solid (see figure A) (1.79 g, 79%, theoretical loading 3.98 mMol/g).

For production of the quaternary ammonim salt polymer **4**, polymer **3** (1 g) was added to methyl iodide (10 equivalents, 39.8 mMol, 5.65g, 2.5 ml), THF (16 ml) and DCM (10 ml)

5    and refluxed (85 $^\circ$C) under a nitrogen atmosphere for 1 hr. The polymer was then transferred to a glass funnel with frit and washed with DCM (3 x 20 ml) and diethyl ether (3 x 20 ml) before being dried under vacumn (1.44 g, 92%).

Elemental C:H:N:I analysis gave: 50.64% C, 7.48% H, 5.77% N and 27.34% I (expected values calculated from a "theoretical" monomer unit of $C_{14.44}H_{24.78}N_{1.85}O_{0.93}I_{0.93}$, formula

10    weight = 356.5 were: 48.66% C, 6.95% H, 7.22% N, and 32.95% I).

### Example 4: *Testing of ROMP fluoride extraction polymer for extraction of fluoride from target water*

1.5 ml of aqueous $^{18}$F-fluoride (i.e. mixture direct from target) measuring approximately 3 MBq (3 mCi) was loaded into a 2.5 ml plastic funnel (Mobitec column, see Figure 4B)

15    containing 0.1 g resin and the mixture agitated for 40 minutes. A further three additional funnels containing silica, tertiary amine resin (**1** Figure 4A) and solid phase removed from a Waters Accell$^{TM}$ QMA Sep-Pack (**3** Figure 4A) were also loaded with aqueous $^{18}$F-fluoride and treated analogously. These served as a control and two comparison groups respectively. After agitation the columns were purged of liquid and flushed with

20    water (3 x 1ml). Both the radioactivity retained on the solid phase as well as that flushed from the funnel was measured.

A representative set of results is shown in the table below.

| Solid phase | Activity retained on resin after water wash. | Activity retained on resin after wash with 1M $K_2CO_3$ (aq) |
|---|---|---|
| Tertiary amine **1** | 45 % | - |
| quaternary-ammonium resin **2** | 91 % | 22 % |
| QMA resin **3** | 94 % | 5 % |
| Silica | 7 % | - |

Though the above results established resin function, direct comparisons of extraction efficiency between resins **2** and **3** (Figure 4A) were approximate due to the difference in

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respective counter ions (iodide & chloride    respectively). To remedy this, the

experiment was repeated with the QMA and quaternary ammonium resins after they

were each conditioned with 1M $K_2CO_3$ (3 x 1ml) and water (3 x 1 ml). This meant that

both resins were in the carbonate form were by a direct comparison could be made. The

5    table below shows a set of representative results.

| Solid phase | Activity retained on resin after water wash. | Activity retained on resin after wash with 1M $K_2CO_3$ (aq.) |
|---|---|---|
| quaternary-ammonium carbonate resin | 39 % | 24 % |
| QMA carbonate resin | 14 % | 28 % |

Extraction of $^{18}$F-fluoride from aqueous media is achieved via the process of ion-

exchange as shown in Figure 4C.


**Example 5:   Cartridge testing of ROMP fluoride extraction polymer for extraction of fluoride from target water**

10    The set up for conducting this experiment is illustrated in Figure 5. The set up consists

of a HPLC pump (2) that supplies a continuous flow of acetonitrile (1) through a HPLC

injection valve (3) and onto the column containing the resin (5). Reagents including:

water, $K_2CO_3$ (aq) and aqueous $^{18}$F-fluoride are contacted with the resin by loading onto

a 2 ml stainless steel loop before being injected (as a liquid plug) into the acetonitrile

15    stream by switching the valve. Liquid output from the column and waste from the loop

are collected in containers (10) and (4) respectively. The column can be heated to a

preset temperature using a heating system, made up of a moulded aluminium block (6),

a thermocouple (8), a band heater (7) and a temperature controller (9). The resin is kept

within the column (5) using PTFE frits (filter discs) at both the column input and column

20    output.


The basic fluoride extraction/recovery experiment conducted on the column proceeded

as follows. Dry ammonium resin (chloride salt) (0.15 g) was loaded onto the column and

the system assembled. The HPLC pump was then set to adminster a continuous flow of

acetonitrile at a flow rate of 0.5 ml/min. At this flow rate the resin was conditioned with

25    plugs of $K_2CO_3$ 0.5 M (3 x 2 ml) and water (3 x 2 ml) each injected via the loop/HPLC

valve. The acetonitrile flow was then reduced to 0.2 ml/min and $^{18}$F-fluoride

approximately 370 MBq (10 mCi) made up to 1 ml with water was injected onto the

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column. After 15 min the flow was            increased to 0.5 ml/min for a further 5

minutes after which the Radioactivity in the collection vial (10) was measured. The

percentage activity that passed through the column without being extracted was

consistently <1 %. Next the output vial (10) was refreshed and the resin flushed with 2

5    ml of $K_2CO_3$ 0.5M at 0.5 ml/min. This step exchanged the fluoride immobilized on the

resin with carbonate causing the radioactivity to leave the column and be recovered in

the collection vial. Using this method it was possible to retain fluoride on the resin and

then subsequently recover it into 0.5 M $K_2CO_3$ (2 ml) at efficiencies averaging 98 %.


### Example 6:  Production of [$^{18}$F]FDG on a microfabricated device

10   The method for extracting the fluoride onto the resin was achieved as detailed in

Example 5.  Having injected the aqueous fluoride onto the column (t = 0 min) at 0.2

ml/min over a period of 15 min, the column was heated to 100 °C, for a further 15

minutes while maintaining the flow of acetonitrile.  This procedure was designed to

azeotropically remove all water from the column.  Then at t = 30 min the loop was

15   flushed with anhydrous acetonitrile and the set temperature reduced to 75 °C. On

attainment of the set temperature (t = X min ) a solution of 1 (20 mg in 1 ml $CH_3CN$;

Figure 6A) was loaded onto the loop and injected onto the column. Lastly at t = X+20

the column was flushed with $K_2CO_3$ (aq) 0.5 M (2M).  This procedure is summarized in

the time-line shown below.



20
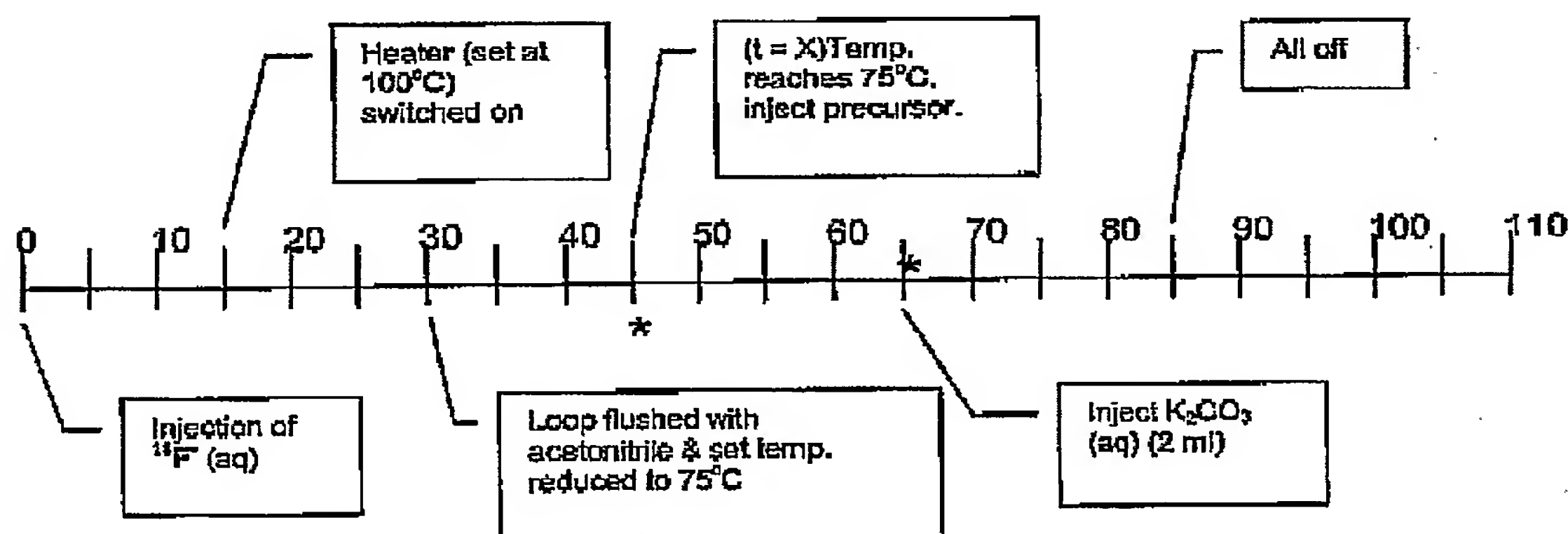
The horizontal scale is in minutes, along which are marked the various operations. The

"*" marks denote points when the column output vial was refreshed. Note also that the

entire process is conducted with a continuous flow of acetonitrile (0.2 ml/min).

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Less than 2 % of the overall radioactivity       eluted from the column (/resin) prior to introduction of the $K_2CO_3$ (aq). With the introduction of $K_2CO_3$ (aq) onto the resin the radioactivity was almost quantitatively eluted into the collection vial (ca 99 %). The radiochemical composition of the collection vial contents was then determined using
5      radio-HPLC. See sample trace in Figure 6B.

Over the course of 4 experiments using the same resin sample a greater percentage of the activity was seen to elute from the column prior to the base flush. By the 4th experiment this percentage had grown to approximately half the total activity. This change-in-behaviour-was-associated-with a discolouration of the resin (despite
10     conditioning prior to each experiment) and a trend to ever less efficient fluoride extraction (see Figure 6C).

**Example 7:   Creation of a predetermined network of microchannels on the surface of a glass, silicon or polymer substrate**

Figure 7 illustrates the steps involved in the creation of a predetermined network of
15     microchannels on the surface of a glass, silicon or polymer substrate.

Masks made using a direct write lithography system were used to shadow cast (expose) substrates.   After shadow casting, the exposed area of photoresist and subsequently chromium were selectively removed.   Next etching using an aqueous solution 5 % (7:1 $NH_4F:HF$), 9.25 % HCL were used to create open channels (etch rates of 0.2 $\mu m$ min$^{-1}$)
20     OF 50 $\mu m$ depth.   Following etching, both resist and chromium layers were removed. To complete the process a pre-drilled cover plate (microscope slide) and etched substrate were sonicated in DMF, acetone and methanol (2 min each) and immersed in conc. sulphuric acid (2hrs). Further washing with ultra pure water and drying under a flow of nitrogen, preceded loading of the furnace.   Thermal bonding used a 12 hr ramped
25     temperature programme with a maximum temperature of 600°C.

76 mm Low Reflective Chrome (Cr 1000⊕), print grade sensitised, Soda Lime glass substrates of thickness 0.01" and 0.06" were purchased from Nanofilm (Westlake Village, Canada).   Clear Soda-lime glass microscope slide 26 mm x 75 mm x 1 mm, hydrochloric acid (HCl), acetone, methanol, ammonium fluoride solution ($NH_4F$),
30     hydrofluoric acid (HF) and sulphuric acid ($H_2SO_4$ sp.gr. 1.84) were purchased from

20

BDH.    Dimethylformamide (DMF) was purchased from Aldrich.    Shipley's
Microposit 351 developer and Shipley's chrome etchant 18 were purchased through
Chestech Ltd. (Chestech Ltd., Rugby, Warwickshire, UK).  Teflon tubing 1.6 mm (1/16")
o.d. 380 µm i.d. was supplied by Upchurch Scientific. GlasSeal Connectors, 1.6 mm

5    (1/16") steel unions, peek fingertight fittings and fused silica capillary (375 µm o.d.) were
supplied by Supelco. Araldite 2014 epoxy was supplied by RS-Components.

Chip design was done on a PC running AutoCad LT for Windows 95.  The Direct Write
Laser system was a prototype DWLII system from Heidelberg Instruments (Heidelberg
Instruments Mikrotechnik GmbH, 69126 Heidelberg, Germany).  Furnace used for glass

10    bonding were  Thermicon P (Heraeus) instruments.

### Example 8:    Coating the surfaces of a microfabricated device with ROMP polymer having tetraalkylammonium side chains

A solution of the monomer Compound 1(Figure 8), crosslinker and catalyst in
tetrahydrofuran was introduced into the device, which was heated using a chromium

15    electrode and an applied voltage of 120 V (~80 °C) to allow polymerisation to occur on
the internal surfaces of the device.  At the same time a stream of nitrogen was flowed
through the microchannels such that the polymer did not block the microchannels
(Figure 9).  The nitrogen supply was at 1.5 Bar (1-2ml/min approx) and the liquid flow
was 5-10 µl/min.  The width of the microchannel (not that defined by the gas flow) was

20    150 µm.

Figure 10 shows a schematic of a microfabricated device as well as micrographs at x25
and x100 of the microchannels coated with ROMP polymer.

The trialkylammonium group on the polymer (compound 2) was then converted to a
tetraalkylammonium group (compound 3) in situ by methylation as shown in Figure 8.

25    ### Example 9:    Recovery of [$^{18}$F]fluoride from $^{18}$O-enriched water

Into the device prepared according to Example 8 was introduced an aqueous solution of
[$^{18}$F]fluoride.  As this passed through the microchannels the [$^{18}$F]fluoride was retained
on the polymer through ion exchange (as illustrated in Figure 11) and enriched water
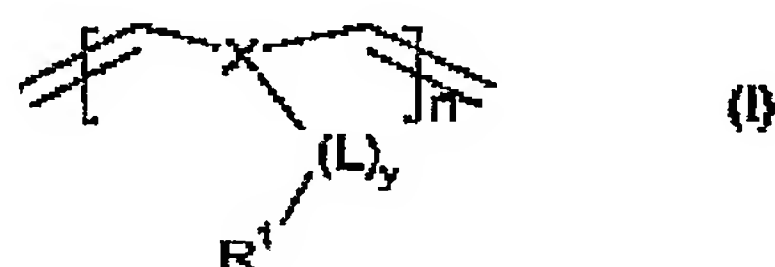was recovered from the exit port of the device.

The polymer can be dried by passing anhydrous acetonitrile through the microchannels with heating.

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## Claims

1) A device adapted to carry out a solid-phase radiochemical process characterised in that the solid-phase radiochemical process is carried out on the internal surfaces of said device wherein said internal surfaces are coated with a Ring Opening Metathesis Polymerisation (ROMP) polymer.

2) The device of claim 1 wherein the ROMP polymer is of Formula I:



(I)

wherein:

X is either a $C_{1-6}$ hydrocarbon chain or a $C_{4-6}$ alicyclic group;

$R^1$ is selected from hydrogen, hydroxyl, halogen, nitro, cyano, -SH, -N=C=O, $C_{1-20}$ alkyl, $C_{4-12}$ aryl, $C_{3-20}$ alkylaryl, $C_{2-20}$ acyl, $C_{2-20}$ functionalised acyl, $C_{1-20}$ formyl, $C_{1-20}$ functionalised formyl, $C_{1-20}$ alkoxy, $C_{1-20}$ functionalised alkoxy, $C_{1-20}$ amino, $C_{1-20}$ functionalised amino, $C_{3-18}$ trialkylammonium, $C_{3-18}$ trialkylammonium with bound fluoride ion, $C_{1-20}$ imino, $C_{1-20}$ functionalised imino, $C_{1-20}$ amido, $C_{1-20}$ functionalised amido, $C_{1-20}$ nitroalkyl, $C_{1-20}$ functionalised nitroalkyl, $C_{1-20}$ carboxyl, $C_{1-20}$ functionalised carboxyl, carbonate, $C_{2-20}$ carboalkoxy or $C_{2-20}$ functionalised carboalkoxy or $R^1$ optionally further comprises a radiotracer precursor, a catalyst or an enzyme;

-$(L)_y$- is linker group wherein each L is independently -$CY_2$- , -CY=CY- , -C≡C- , -$CY_2CO_2$- , -$CO_2CY_2$- , -NYCO- , -CONY- , -NY(C=O)NY-, -NY(C=S)NY-, -$SO_2$NY- , -$NYSO_2$- , -$CY_2OCY_2$- , -$CY_2SCY_2$- , -$CY_2NYCY_2$- , a $C_{4-8}$ cycloheteroalkylene group, a $C_{4-8}$ cycloalkylene group, a $C_{5-12}$ arylene group, or a $C_{3-12}$ heteroarylene group, or an amino acid, wherein Y is independently chosen from H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ alkoxyalkyl or $C_{1-4}$ hydroxyalkyl and y is an integer of value 0 to 10; L is optionally further substituted with one or more $R^2$ groups where $R^2$ is selected from hydrogen, hydroxyl, halogen, nitro, cyano, -SH, —

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N=C=O, $C_{1-20}$ alkyl, $C_{4-12}$ aryl, $C_{3-20}$     alkylaryl, $C_{2-20}$ acyl, $C_{2-20}$ functionalised acyl, $C_{1-20}$ formyl, $C_{1-20}$ functionalised formyl, $C_{1-20}$ alkoxy, $C_{1-20}$ functionalised alkoxy, $C_{1-20}$ amino, $C_{1-20}$ functionalised amino, $C_{3-18}$ trialkylammonium, $C_{1-20}$ imino, $C_{1-20}$ functionalised imino, $C_{1-20}$ amido, $C_{1-20}$ functionalised amido, $C_{1-20}$

5   nitroalkyl, $C_{1-20}$ functionalised nitroalkyl, $C_{1-20}$ carboxyl, $C_{1-20}$ functionalised carboxyl, carbonate, $C_{2-20}$ carboalkoxy or $C_{2-20}$ functionalised carboalkoxy; and,

n = number of polymer units.

3)  The device of claim 1 wherein the ROMP polymer is of Formula II:



(II)
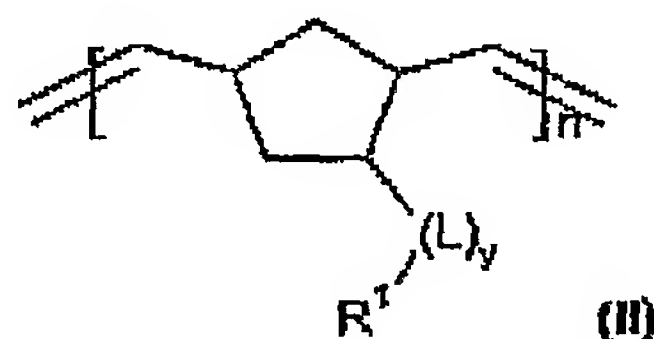
10   wherein:

-(L)$_y$-, $R^1$ and n are as defined in claim 2 for Formula I.

4)  The device of claim 1 wherein the ROMP polymer is of Formula III:
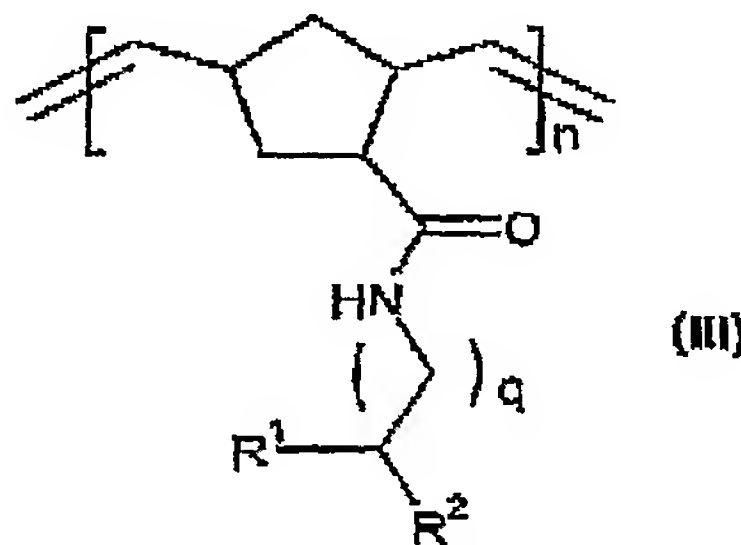


(III)

wherein:

15   $R^1$ and n are as defined in claim 2 for Formula I;

$R^2$ is an optional group as defined in claim 2 for -(L)$_y$- of Formula I; and,

q = 1-4.

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5) The device of any of claims 1-4               wherein R¹ is a group suitable for binding an $^{18}F$-fluoride ion.

6) The device of claim 5 wherein R is a trialkylammonium group of Formula IV:

$$-N^{+}R^{3}R^{4}R^{5}    \qquad (IV)$$

5       wherein $R^{3-5}$ are each independently a $C_{1-6}$ alkyl group.

7) The device of either of claims 5 or 6 further comprising a bound $^{18}F$-fluoride ion.

8) The device of any of claims 1-4 wherein R¹ is a $C_{1-20}$ alkyl group.

9) The device of any of claims 1-4 wherein R¹ is –N=C=O.

10) The device of any of claims 1-4 wherein R is a group comprising an enzyme.

10      11) The device of any of claims 1-4 wherein R¹ is -SH.

12) The device of any of claims 1-11 which is a microfabricated device.

13) A method for the production of the device of claim 12 comprising:

   (i)     creating a defined network of microchannels within said device;

   (ii)    heating the device to a temperature of between 80°C and 140°C; and,

15   (iii)   passing a solution of monomer, crosslinker and catalyst through the microchannels while concurrently introducing a flow of nitrogen through the microchannels such that ROMP polymer is deposited on walls and indentations of the microchannels.

14) The method of claim 13 wherein step (i) comprises:

20      (a) providing a suitable substrate;

   (b) marking a specific pattern onto the surface of said substrate;

   (c) etching the pattern into the surface of said substrate; and

   (d) attaching a cover to the etched surface of step (c) thereby forming channels.

25

15) The method of claim 13 wherein step (i) comprises the use of a polymer in a process selected from injection moulding, hot embossing, casting, lithography or machining.

16) An automated synthesis system comprising a series of interconnected devices wherein each device is a device according to claims 1-12 wherein said devices are:

   (i) a mixing and reaction device;

   (ii) an analysis device; and,

   (iii) a separation device.

17) Use of the device of any of claims 1 to 12 for:

   (i) recovery of radioisotopes;

   (ii) radiochemical synthesis; or

   (iii) radiochemical purification.

18) The use of claim 17 wherein said recovery of radioisotopes is recovery of $^{18}$F-fluoride ion from $^{18}$O-enriched water containing $^{18}$F-fluoride ion or natural water containing $^{18}$F-fluoride ion.

19) The use of claim 18 wherein said device is a device according to either of claims 5 or 6.

20) The use of either of claims 18 or 19 wherein the recovered $^{18}$F-fluoride ion is used for a radiofluoridation reaction *in situ* or is recovered in a suitable solvent.

21) The use of claim 17 wherein said radiochemical synthesis is an enzymatic chemical reaction.

22) The use of claim 17 wherein said radiochemical synthesis is a radiofluoridation.

23) The use of claim 22 wherein the radiofluoridation forms a step in the production of an $^{18}$F-labelled radiotracer.

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24) The use of claim 23 wherein said $^{18}$F-          labelled radiotracer is $^{18}$F-FDG, $^{18}$F-FDDNP, $^{18}$F-F-DOPA or $^{18}$F-FLT.

25) The use of any of claims 22 to 24 wherein said device is a device according to claim 7.

5   26) The use of claim 17 wherein said radiochemical purification comprises chromatographic separation.

27) The use of claim 17 wherein said radiochemical purification is removal of secondary amine, hydroxyl or thiol from alkylation reactions wherein the alkylated product is radiolabelled.

10  28) A process for labelling the precursor of a radiotracer with a radiolabel characterised in that the radiolabel is provided bound to a ROMP polymer.

29) A process for labelling the precursor of a radiotracer with a radiolabel characterised in that the precursor is provided bound to a ROMP polymer.

30) The process of either of claims 28 or 29 wherein said radiotracer is $^{18}$F, $^{11}$C, $^{99m}$Tc.

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## Abstract

The present invention involves the application of ROMP polymers to the internal
surfaces of a device for the purpose of carrying out a solid-phase radiochemical process
within the device.  An additional embodiment of the invention is an automated synthesis

5    system comprising a number of devices of the invention in order that a series of
processes can be carried out in direct sequence.  In a preferred embodiment, the
present invention is a microfabricated device.

Figure 1

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Figure 2

**Figure 3**
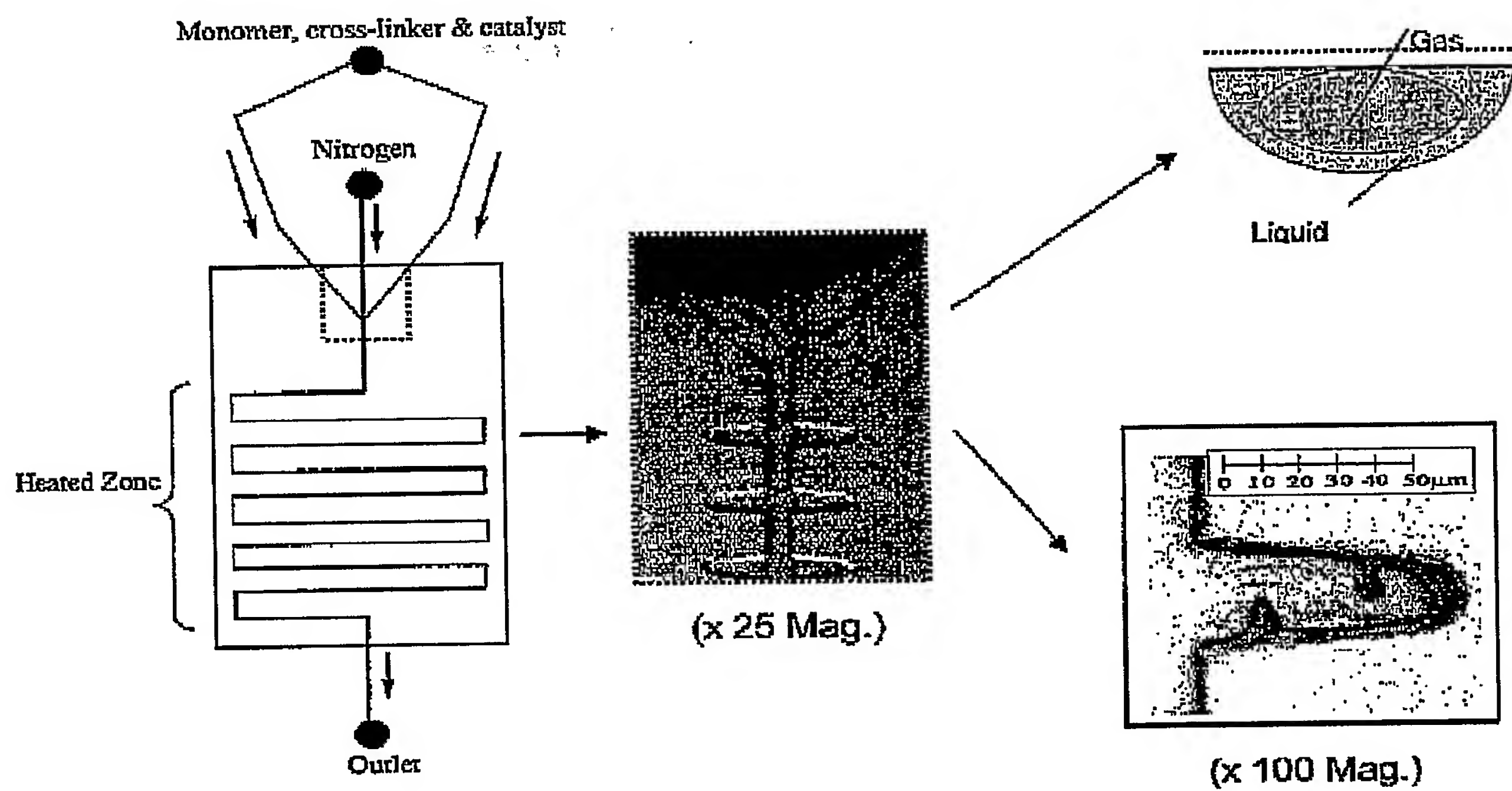
(A)



(B)



(C)

**Figure 4**

**Figure 5**

(A)



(B)



(C)

**Figure 6**

**Figure 7**

Figure 8

Figure 9

Figure 10

**Figure 11**